ES 221 Problem Set 3

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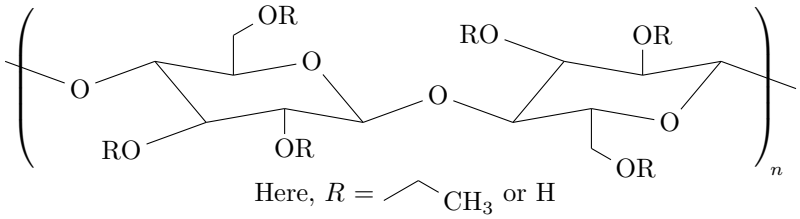
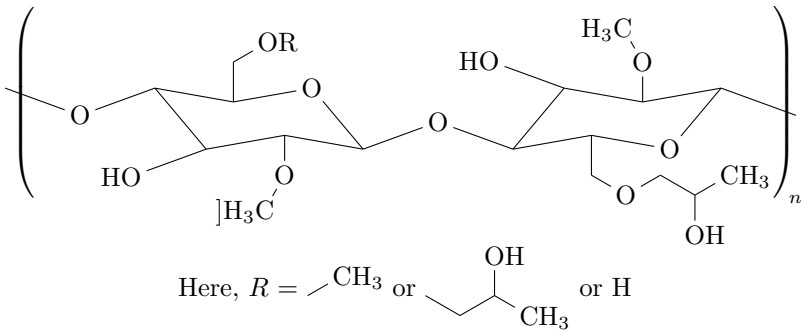
22 April 2020

1 Question 1: Matrix Polymers for Extended Release Tablets

The novel antiretroviral massvirone has displayed excellent efficacy and broad applicability to a number of different viral strains. However, the short half-life of 1.2 hours has necessitated a dosage of 10 mg, 6 times per day for such clinical efficacy. Thus, there is a clear need for an extended release system that permits administration at a higher dose (30 mg) and lower frequency (twice a day). Three different prototype extended release systems are studied below, including 1) hydrophobic polymer release, 2) hydrophilic polymer matrix erosion, and 3) an osmotic push/pull system. These three systems rely on matrices constructed from 1) ethyl cellulose, 2) hydroxypropyl methylcellulose (HPMC), and 3) polyethylene oxide (PEO), respectively. The trade names of these polymers are $ETHOCEL^{TM}$, $Methocel^{TM}$, and $POLYOX^{TM}$, respectively.

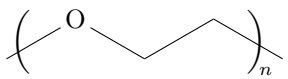


The chemical structure above shows the functional repeat unit for the ethyl cellulose molecule. The cellulose molecule is a hydrophilic polysaccharide commonly found in plant cell walls consisting of alternating D-glucose rings linked together by $\beta(1-4)$ ether linkages (i.e. the location of the side groups of each alternating ring are flipped relative to its neighboring rings). In the regular cellulose molecule, there are three hydroxyl groups coming off of the main ring (in actuality, one of these is a hydroxymethyl). In the ethyl cellulose molecule, some of the hydrogen atoms in the hydroxyl and hydroxymethyl groups are substitutued with ethyl groups, i.e. CH_2CH_3. The ring nature of the cellulose molecule confers some intrisinsic hydrophobicity, but the presence of hydroxyl groups allows for hydrogen-bonding either with other cellulose chains or with surrounding water molecules, providing hydrophilic character. Subsituting these with ethyl groups, however, removes the ability to hydrogen-bond, making ethyl cellulose substantially more hydrophobic than its non-substituted counterpart. As a result, it is an excellent choice for a hydrophobic release system, in which the matrix serves to form a diffusion-limited kinetic scheme. Drug molecules close to the depleted edge of the polymer matrix will diffuse out with a rate determined by the local polymer chain structure. This can be modeled as a moving-boundary problem, in which the boundary between the "constant" drug concentration and the "depleting" region moves as drug diffuses out.



Hydroxypropyl methylcellulose, like ethyl cellulose, is a cellulose derivative with subsitutions at the same three oxygen atoms. In this case, however, the subtituted hydrogens can be either methyl groups (CH_3) or hydroxypropyl groups ($CH_2CHOHCH_3$), in addition to the unsubtituted hydroxyl groups. While the methyl groups do remove ability to hydrogen-bond, this is made up for by the remaining hydroxyl groups, as well as those on the hydroxypropyl substitutions. As a result, HPMC is more hydrophilic than ethyl cellulose and is commonly used for extended release through swelling and erosion. In this case, the hydrophilic nature will allow water to infiltrate the polymer, causing swelling which frees trapped drug molecules. In principle, the system can be viewed as three interacting subsystems- an inner dry layer, containing its full drug load; a middle dissolving layer from which drug is currently diffusing; and an outer eroded layer which has been entirely swollen and in which no drug remains. A highly hydrophilic molecule

would rapidly swell, leading to an erosion/dissolution-dependent system, while less hydrophilicity pushes release closer to that of the moving boundary case. Thus, by controlling the degree of substitutions of HPMC, as well as the fraction of each substituted group, the kinetics of release can be altered to fall in a different place between zero-order kinetics and square-root time dependence. Similarly, the molecular weight of HPMC can also be controlled. Higher molecular weight structures will be more entangled, mimicking a cross-linked structure, and will thus take longer to relax and allow drug to escape.



Polyethylene oxide (PEO) is a simpler polymer than the cellulose derivatives, containing ethyl groups linked through ethers. The oxygen permits hydrogen bonding, and due to its relatively small structure, PEO is a hydrophilic molecule in general. As a result, PEO is an excellent choice for an osmotic push-pull system, which relies on the diffusion of water to create an osmotic pressure gradient. In these systems, a high molecular weight polymer containing an osmogen like sodium chloride swells without allowing drug diffusion, pushing on a lower molecular weight polymer containing drug. The pressure generated by this expansion causes drug to be released through a small hole through the outer semipermeable membrane on the tablet. PEO can be obtained in a wide variety of molecular weights, and its hydrophilic nature will allow it to swell and generate the osmotic force in the expansion layer.

2 Question 2: *In Vitro* Release Kinetics of Massvirone Tablets

With the above materials chosen for the three polymeric release systems, 500-tablet lots of each drug delivery system were synthesized and loaded. Hot melt extrustion was used for the hydrophobic system, and wet granulation and coating for the remaining two. *In vitro* release experiments were performed for each formulation at a pH of 6.0 at body temperature with a $30mg$ dose. The cumulative release percentage at each time point was recorded over the course of 16 hours. To estimate a power-law fit for each of the three extended release systems, data was considered for all points below a release fraction of 0.90. It should be noted that only one data point for the immediate release system is below this threshold, so a power-law fit could not be performed. Even so, an immediate release drug is not expected to follow power law kinetics anyway. The natural logarithm was taken of both sides to linearize the equation, and linear regression was used to extract the rate constant, k, and diffusional exponent, n, for each of the systems.

$$\frac{M_t}{M_0} = kt^n \tag{1}$$

$$\ln \frac{M_t}{M_0} = \ln k + n * \ln t \tag{2}$$

Figure 1 shows the fitted power-law release profiles for each extended release system. The diffusional exponents are found to be 0.448, 0.768, and 1.12 for the ethyl cellulose hydrophobic release, HPMC matrix erosion, and PEO osmotic pump system, respectively. These values are approximately consistent with the expected mechanism of release, as a hydrophobic release system is expected to undergo Fickian diffusive release characteristic of a moving-boundary problem ($n = 0.5$), a hydrophilic system mediated by polymer swelling and erosion is expected to follow so-called anomalous transport kinetics (having a diffusional exponent between the two extremes given that this reflects a balancing of diffusion of drug through the matrix and dissolution of the matrix into the surrounding solution), and an osmotic pump system should follow zero-order kinetics ($n = 1.0$). These are consistent with the obtained values, though experimental errors of around 10% appear to be present for the limiting cases. It is likely that these are due to a number of factors, including inaccuracies in measurement (as total fractional release exceeded 100% in some cases), limited data since only values up to 90% were used, and the fact that, of course, any physical system will exhibit a mix of release mechanisms.

We can also estimate the duration of release using the half-life. As is standard, the half-life can be defined as the time for 50% of the total drug to be released. By setting the left-hand side of the above logarithmic equation equal to 50 (as this was fit using the percentage as the dependent variable), we can calculate the half-life, $t_{1/2}$, as:

$$t_{1/2} = e^{\frac{\ln 50 - \ln k}{n}} \tag{3}$$

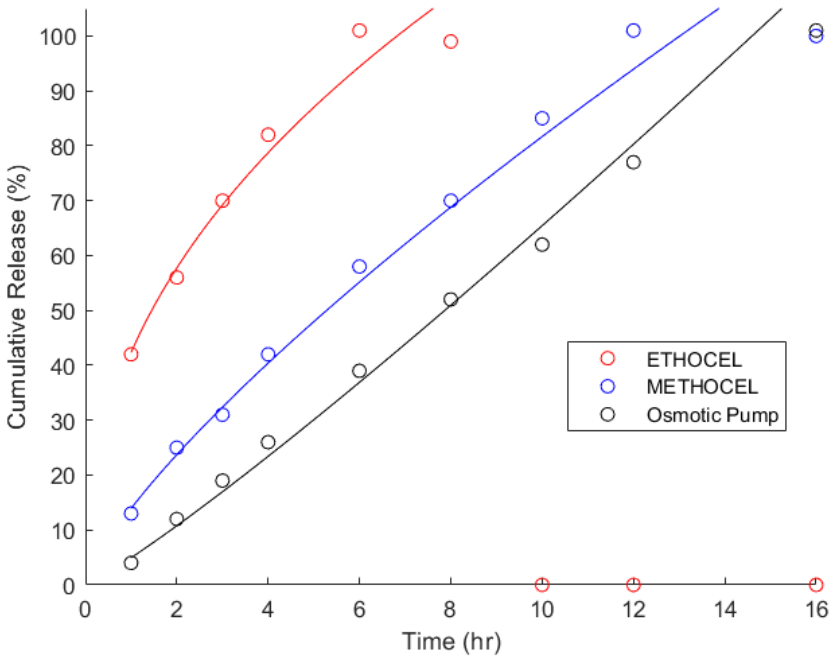


Figure 1: Power Law Fits for Each Extended Release System.

This analysis yields half-lives of $1.45hr$, $5.28hr$, and $7.87hr$ for the hydrophobic release, polymer erosion, and osmotic pump systems, respectively, which is consistent with what could be estimated from the plots. However, half-life as a measure for duration of release is less well-defined for power law systems than for typical exponentials, so these values must be taken with caution. For example, despite the approximately 5.2-fold higher half life of the osmotic pump system over the hydrophobic release, the time required to reach 100% release as predicted by the power-law model is approximately 3.4-fold higher for the osmotic pump.

3 Question 3: Pharmacokinetics of Massvirone Extended Release Tablets

A phase one human study trial was initiated using the above three extended release systems at the $30mg$ dose and the current $10mg$ immediate release system. Plasma levels were measured over the course of 24 hours. The resulting data is presented in Figure 2, which also contains a piecewise cubic Hermitic interpolating polynomial (PCHIP) interpolation as used previously for complex plasma concentration data. Other interpolation methods were not investigated, as this appears to do an acceptable job at recapitulating the experimental data points. Three requirements were put forth for a successful extended release candidate: The drug must have a relative exposure of at least 0.90 relative to the immediate release formulation; the maximum concentration must not exceed that of the immediate release tablet, and the time above a threshold concentration of $40ng/mL$, a factor of ten higher than the *in vitro* inhibitory concentration, must exceed 10 hours. For the first criterion, the relative exposure is defined by the ratios of the area under the curve, which is estimated using Matlab's trapz function. This function uses the trapezoidal rule on the data to approximate the integral:

$$\int_a^b f(x)dx \approx \frac{1}{2}\Sigma_{n=1}^{N}(x_{n+1} - x_n)[f(x_{n+1} + f(x_n)] \tag{4}$$

From this, we can calculate the relative exposure for the three extended release systems as 1.13, 1.14, and 0.86. Thus, the osmotic pump system does not release a sufficient amount of drug over the 24 hours. From the second criterion, it is clear that the hydrophobic release system will not work as desired, as it reaches a maximum concentration 1.5-fold higher than the immediate release. The other two formulations meet this specification. The time above the therapeutic threshold can be estimated from the interpolation function or from the data itself. In either case, we obtain values of 4.2, 8.25, 12.9, and $11.6hr$ for the immediate release and the three extended release in the order they have previously been listed. Again, the hydrophobic release does not meet this specification. Thus, the only drug which meets all three criteria is the hydrophilic polymer swelling/erosion system.

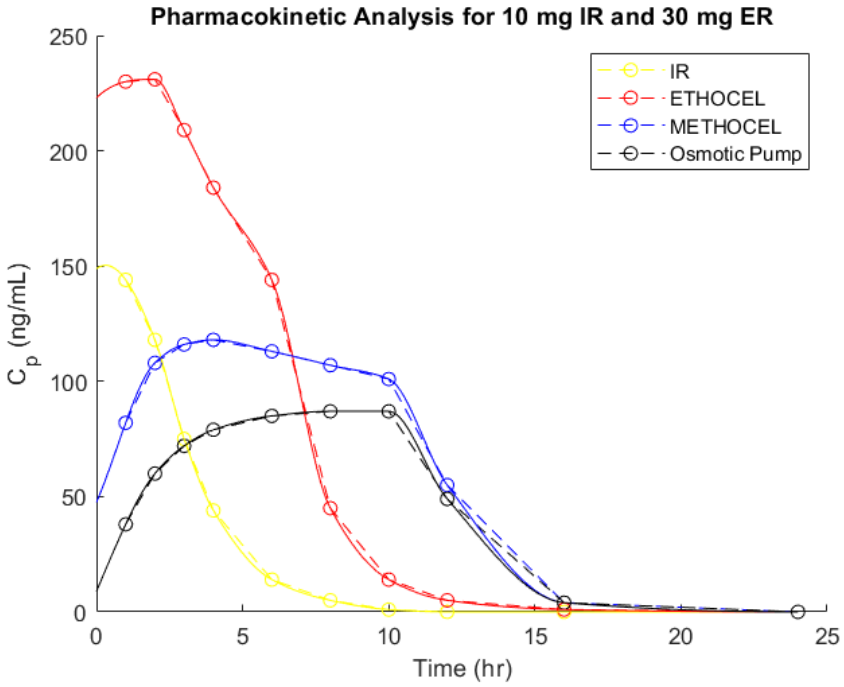


Figure 2: Interpolated Time Course of Plasma Concentration for Each Release System using Pchip.

4 Appendix

Script to perform power law fits on cumulative release percentage of drug from extended release systems. The script takes the natual logarithm of both sides and uses linear regression to extract the fit parameters for all data less than 0.9 cumulative release fraction. The model is then used to predict the time course of release for visualization. The half life and power law exponent are also extracted.

```
t = [1,2,3,4,6,8,10,12,16];
DER = 30; %mg

fit = zeros(3,2);

RETH = [42,56,70,82,101,99];
tvalid = t(1:length(RETH<0.9));
fit(1,:) = polyfit(log(tvalid),log(RETH(1:length(tvalid))),1);

RMETH = [13,25,31,42,58,70,85,101,100];
tvalid = t(1:length(RMETH<0.9));
fit(2,:) = polyfit(log(tvalid),log(RMETH(1:length(tvalid))),1);

ROS = [4,12,19,26,39,52,62,77,101];
tvalid = t(1:length(ROS<0.9));
fit(3,:) = polyfit(log(tvalid),log(ROS(1:length(tvalid))),1);

n = fit(:,1);

tpredict = 1:0.05:16;
Mpredict = zeros(3,length(tpredict));
figure;
hold on;
sz = 25;
scatter(t,[RETH,zeros(length(t)-length(RETH),1)'],'r');
```

```
scatter(t,[RMETH,zeros(length(t)-length(RMETH),1)'],'b');
scatter(t,[ROS,zeros(length(t)-length(ROS),1)'],'k');
colors = ['r';'b';'k'];
for i = 1:3
    Mpredict(i,:) = exp(fit(i,2))*tpredict.^(n(i));
    plot(tpredict,Mpredict(i,:),colors(i));
end
ylim([0 105])
xlabel('Time (hr)');
ylabel('Cumulative Release (%)');
legend({'ETHOCEL','METHOCEL','Osmotic Pump'});
lt12 = (log(50)-fit(:,2))./n;
t12 = exp(lt12);
```

Script to calculate AUC for each release system using the trapezoidal rule. AUC is then normalized by dose and to the immediate release system to calculate relative exposure. A pchip interpolation is also performed on each data set, which is used to determine the maximum plasma concentration and the time above the therapeutic dose (a factor of 10 above the in vitro inhibitory concentration).

```
t = [1,2,3,4,6,8,10,12,16,24];
time = 0:0.05:24;
DIR = 10*10^6;
DER = 30*10^6;
D = [DIR,DER,DER,DER];

Cp =
    [144,118,75,44,14,5,1,0,0,0;230,231,209,184,144,45,14,5,1,0;82,108,116,118,113,107,101


figure;
hold on;
numform = size(Cp,1);
AUC = zeros(size(Cp,1),1);
AUCnorm = AUC;
RelExp = AUCnorm;
I = zeros(size(Cp,1),length(time));
Cmax = AUC;
Cmaxnorm = Cmax;
tabove40 = Cmax;
colors = ['y';'r';'b';'k'];
for i = 1:numform
    plot(t,Cp(i,:),['--o',colors(i)]);
    AUC(i) = trapz(t,Cp(i,:));
    AUCnorm(i) = AUC(i)./D(i);
    RelExp(i) = AUCnorm(i)/AUCnorm(1);
    I(i,:) = interp1(t,Cp(i,:),time,'pchip');
    Cmax(i) = max(I(i,:));
    Cmaxnorm(i) = Cmax(i)/Cmax(1);
    tabove40(i) = 0.05*sum(I(i,:)>40);
end
for i = 1:numform
     plot(time,I(i,:),colors(i));
end
xlabel('Time (hr)');
ylabel(['C_p (ng/mL)']);
title('Pharmacokinetic Analysis for 10 mg IR and 30 mg ER');
legend({'IR','ETHOCEL','METHOCEL','Osmotic Pump'});
tabove40data = [4;8;12;11];
```